Outbreak of measles in a highly vaccinated secondary school population

Penny A. Sutcliffe, MD, MHSc; Elizabeth Rea, MD, MSc, FRCPC

Abstract • Résumé

Objective: To examine the factors associated with measles vaccine effectiveness and the effect of two doses of vaccine on measles susceptibility during an outbreak.

Design: Retrospective cohort study.

Setting: A secondary school in the City of Toronto.

Subjects: The entire school population (1135 students 14 to 21 years of age).

Main outcome measures: Risk of measles during an outbreak associated with age at first measles vaccination, length of time since vaccination, vaccination before 1980 and whether date of vaccination was estimated; vaccine efficacy of one dose versus two doses.

Results: Eighty-seven laboratory-confirmed or clinically confirmed cases of measles were identified (for an attack rate of 7.7%). The measles vaccination rate was 94.2%, and 10% of the students had received two doses of measles vaccine before the outbreak. Among those who had received only one dose of vaccine, vaccination at less than 15 months of age was associated with vaccine failure (relative risk 3.62, 95% confidence interval 2.32 to 5.66). There was no increased risk of vaccine failure associated with length of time since vaccination once the relative risk was adjusted for age at vaccination in a stratified analysis. Vaccination before 1980 and an estimated date of vaccination were not associated with increased risk of vaccine failure. Administration of a second dose of vaccine during the outbreak was not protective. Two doses of vaccine given before the outbreak conferred significant protection, and the relative risk of failure after one dose versus two doses was 5.0 (95% confidence interval 1.25 to 20.15). Of the 87 cases, 76 (87%) could have been prevented had all the students received two doses of measles vaccine before the outbreak, with the first at 12 months of age or later.

Conclusions: Delayed primary measles vaccination (at 15 months of age or later) significantly reduced measles risk at later ages. However, revising the timing of the current 12-month dose would leave children vulnerable during a period in which there is increased risk of complications. The findings support a population-based two-dose measles vaccination strategy for optimal measles control and eventual disease elimination.

Objectif : Examiner les facteurs associés à l'efficacité du vaccin antirougeoleux et l'effet de deux doses du vaccin sur la susceptibilité à la rougeole pendant une poussée.

Conception : Étude comparative rétrospective de cohortes.

Contexte : École secondaire de Toronto.

Sujets : Toute la population de l'école (1135 élèves de 14 à 21 ans).

Principales mesures de résultats : Risque de rougeole pendant une poussée associé à l'âge à la première vaccination antirougeoleuse, la période écoulée depuis la vaccination, la vaccination avant

Dr. Sutcliffe is a resident in the Community Medicine Residency Program, University of Toronto, Toronto, Ont., and Dr. Rea is an associate medical officer of health with the Department of Public Health, City of Toronto, Ont.

Reprint requests to: *Dr. Elizabeth Rea, Department of Public Health, City Hall, 100 Queen St. W, Toronto ON M5H 2N2; fax 416 392-0713; erea@pmb.med.utoronto.ca*

← For prescribing information see page 1513

1980 et l'indication ou non d'une date de vaccination estimative; comparaison de l'efficacité d'une et deux doses du vaccin.

Résultats : On a décelé 87 cas de rougeole confirmés par test en laboratoire ou observation clinique (pour un taux d'attaque de 7,7 %). Le taux de vaccination antirougeoleuse s'est établi à 94,2 %, et 10 % des élèves ont reçu deux doses du vaccin avant la poussée. Parmi ceux qui avaient reçu seulement une dose du vaccin, on a associé l'échec du vaccin à une vaccination reçue avant l'âge de 15 mois (risque relatif de 3,62, intervalle de confiance à 95 %, de 2,32 à 5,66). Le risque d'échec du vaccin associé à la période écoulée depuis la vaccination n'a pas augmenté lorsqu'on a rajusté le risque en fonction de l'âge à la vaccination, lors d'une analyse stratifiée. On n'a pas associé à un risque accru d'échec du vaccin une vaccination reçue avant 1980 ni une date estimative de vaccination. L'administration d'une deuxième dose du vaccin pendant la poussée n'a pas eu d'effet protecteur. Deux doses reçues avant la poussée ont conféré une protection appréciable, et le risque d'échec après une dose plutôt que deux a atteint 5,0 (intervalle de confiance à 95 %, de 1,25 à 20,15). Des 87 cas, 76 (87 %) auraient pu être évités si tous les élèves avaient reçu deux doses du vaccin antirougeoleux avant la poussée, le premier à l'âge de 12 mois ou après.

Conclusions : En reportant la première vaccination antirougeoleuse après l'âge de 15 mois, le risque de rougeole diminue largement par la suite. Toutefois, si l'on modifie la date actuelle de vaccination (à l'âge de 12 mois), les enfants seraient alors vulnérables pendant une période où ils courent un risque plus élevé de complications. Les résultats appuient une stratégie de vaccination antirougeoleuse à deux doses dans la population afin d'atteindre une répression optimale de la maladie et son élimination éventuelle.

Measles is a highly communicable disease that is a significant cause of illness and death worldwide.[1,2] In Canada the Consensus Conference on Measles has set a goal of measles elimination by 2005.[3] However, it is predicted that a one-dose vaccination strategy will result in failure to reach this goal, because of the estimated vaccine failure rate of 5% and the high transmissibility of the virus.[4,5] With high vaccination rates in a population, measles becomes a disease affecting vaccinated people; therefore, strategies to reduce vaccine failure rates need to be identified.

Measles vaccine became available in Canada in 1963, and the mean annual incidence of measles fell from 358 per 100 000 during 1949–58 to 18 per 100 000 during 1982–91.[3,6] However, large outbreaks occurred in Quebec in 1989 (10 000 cases) and in Ontario in 1991–92 (8000 cases).[6,7] Ontario had more than 2200 cases in the first three quarters of 1995 and accounted for more than half of all measles cases reported in the Americas during that period.[8,9] In addition to the health costs of measles outbreaks, there are substantial economic and disruptive costs to schools, parents and the medical care and public health systems.[2,10]

Measles vaccination failure may be primary or secondary. Primary failure implies a failure of initial vaccination to produce a protective immune response. Secondary failure refers to inadequate later protection despite successful primary immunization (i.e., waning immunity). Risk factors for vaccine failure examined in previous studies have included early age at vaccination, vaccination before 1980, length of time since vaccination and estimation of date of vaccination (as a proxy for possible early vaccination).[11–13] Debate over the timing of measles vaccination continues: older age (e.g., 15 months) at vaccination results in better immunity, but younger children (12 months) are at greatest risk of complications from measles.[14–17]

The estimated rate of primary measles vaccination failure (for a single dose) is about 5%. However, because measles is highly contagious, herd immunity levels greater than 95% are required to prevent outbreaks.[18] One strategy to further reduce the risk of measles is a routine two-dose measles vaccination program. The rationale for a two-dose program is that, in a well-vaccinated population, it will increase herd immunity levels above the outbreak threshold level.

Although several jurisdictions have introduced routine two-dose measles schedules, few studies have directly assessed the effectiveness of a second dose.[5,19,20] In addition, inconsistencies in practice exist. The United States adopted a two-dose policy in 1989, whereas Canada largely practises a one-dose policy.[21] Despite the recommendation of the Canadian Consensus Conference on Measles for a routine two-dose schedule,[3] only Ontario and Quebec have implemented school-based public health catch-up campaigns to date, with an expected cost in Ontario of $4.5 million.[22,23] [Since the time of writing, British Columbia, Prince Edward Island and the Yukon Territory have initiated catch-up campaigns (late spring 1996) for school-aged children.[24]]

An outbreak of measles in a Toronto secondary school provided an opportunity to conduct a retrospective cohort study of measles vaccine effectiveness. Because of personal preference or advice from physicians, some parents had already opted for two-dose measles vaccination for their children. We could therefore investigate the factors associated with primary measles vaccination that significantly affect the risk of measles in an outbreak as well as the effect of administration of a second dose of vaccine during an outbreak.

Background

The greater Toronto area encompasses 10 health-unit jurisdictions and includes a population of approximately 4.3 million (according to the 1991 census of Canada). Within this area the City of Toronto (population approximately 600 000) has about 100 000 schoolchildren, with an annual turnover in the school population of about 40%. In the spring of 1995 outbreaks of measles began to be reported in the greater Toronto area. By June 30, 1995, the number of confirmed measles cases had climbed to almost 800, of which more than 400 were accounted for by the largest health unit area (Peel Region). In the City of Toronto 177 cases were reported by June 30, almost all in school-aged children. Although most affected schools had only 1 or 2 cases, one secondary school had 87 cases in a student population of 1135 (grades 9 to 13, ages 14 to 21 years).

The investigation of the outbreak in this school included confirmation of measles diagnosis according to the National Advisory Committee on Immunization (NACI) definition[25] or a modified definition (Table 1), investigation of the source of infection, additional case-finding and identification of susceptible people. Susceptible people were defined as those born after 1956 with no history of measles vaccination or laboratory-confirmed illness, or as those with a history of vaccination before their first birthday and no history of illness.[3,25] People born in 1956 or earlier are assumed to have natural immunity.[26]

Outbreak control measures included holding a measles vaccination clinic at the school for susceptible people, at which 33 students were vaccinated, and the subsequent exclusion from school of persistently susceptible people (those who, under Ontario's Immunization of School Pupils Act,[27] have medical, philosophical or religious exemptions from vaccination and have no proof of past measles). Students with measles were excluded for 5 days after the onset of measles rash, and susceptible students for 14 days after the onset of the last measles case in the school, as directed in the NACI outbreak guidelines.[25]

Table 1: National Advisory Committee on Immunization (NACI) definition of measles and modified definition[21]

Confirmed case (NACI)
Detection of measles virus in appropriate specimens; **or**
Fourfold rise in serum antibody titre or the presence of measles-specific IgM; **or**
Clinical measles in a person who is a known contact of a laboratory-confirmed case
Clinical case (NACI)
Temperature ≥ 38.3°C; **and**
Cough, coryza or conjunctivitis; **followed by**
Generalized maculopapular rash for at least 3 days
Modified clinical case
Cough, coryza or conjunctivitis; **followed by**
Generalized maculopapular rash for at least 3 days

Methods

We conducted a retrospective cohort study involving all students registered at the secondary school in Toronto. The distribution of cases by age and by grade did not vary significantly (see Results), and questioning of affected students failed to reveal activity- or location-specific risks. Given these factors and the extremely contagious nature of the measles virus, exposure to measles was assumed to be universal.

Cohort identification

Current student lists are provided to Ontario public health departments by local boards of education and by private schools. This information is merged with student vaccination records (based on written documentation by the health care provider) to form Ontario's computerized Immunization Record Information System (IRIS). These data are collected under the authority of the Immunization of School Pupils Act[27] and are maintained in confidence by public health departments. The database is thought to be highly complete and accurate; however, no studies have been conducted to assess this. The City of Toronto Department of Public Health reviews vaccination records of all its schools annually and of particular schools when a communicable, vaccine-preventable disease occurs in a school-aged child.

Case identification

Measles is a reportable disease in Ontario, and it is the responsibility of physicians and laboratories to notify the local medical officer of health of suspected and confirmed cases.[28,29] In this outbreak, the initial case notification occurred when the health department received laboratory confirmation of measles-specific IgM in a specimen obtained from a student. Additional cases were identified through active case-finding by public health staff and notification by laboratories and physicians. Letters were delivered to all students, informing them of the outbreak and of the symptoms of measles. Students with symptoms were instructed to follow up with their physicians and to contact the health department. Each student with suspected measles was followed by telephone by health department staff to determine whether the illness met the NACI case definition, to identify possible risk activities and contacts, and to confirm the date of disease onset. A modified case definition was applied to three students who reported clinical measles, including fever, but who had failed to record their temperature. Once identified, cases were entered into the province's computerized Reportable Disease Information System. The file from this system was merged with the IRIS database to form a composite file.

Risk-factor assessment

Demographic information (age, sex, grade and classroom) was complete. Age at first measles vaccination, length of time since measles vaccination, date of vaccination, whether date of measles vaccination was estimated and number of vaccine doses were also obtained from the IRIS database.

Statistical analysis

We analysed the data using EpiInfo (version 6.0; US Centers for Disease Control and Prevention, Atlanta). Chi-squared values were calculated for categorical variables, and Student's *t*-tests were conducted for continuous variables. Relative risks (RRs) were calculated for each risk factor examined and were adjusted in a stratified analysis of multiple variables.

The study population was categorized by vaccination status: never vaccinated; vaccinated once, before the outbreak; vaccinated twice, before the outbreak; vaccinated once, during the outbreak; and vaccinated twice, the second dose having been delivered during the outbreak. The number of vaccinees in each category who received their dose before 12 months of age (inadequate vaccination[21]) was also determined.

We calculated vaccine efficacy values comparing the following groups: those never vaccinated with those adequately vaccinated once (vaccination at age 12 months or later); those never vaccinated with those adequately vaccinated twice; and those adequately vaccinated once with those adequately vaccinated twice. Vaccine efficacy is the difference between the attack rate among nonvaccinated subjects and that among vaccinated subjects, divided by the attack rate among nonvaccinated subjects. It is widely used to assess vaccine effectiveness.[14] Vaccine efficacy estimates may range up to 100% when the attack rate in the vaccinated population is 0% but have no theoretical lower limit if the risk of disease in vaccinated people is greater than the risk in nonvaccinated people.

We determined the number of preventable measles cases by taking the difference between the observed and expected numbers of cases in the subgroups of interest. Expected numbers of cases were calculated by applying the attack rate observed in the subgroups to the total school population.

Results

Descriptive analysis

Measles was diagnosed in 87 students (47 boys and 40 girls) at the school between Apr. 13 and June 12, 1995. Of the 87 cases 14 (16.1%) were laboratory confirmed, 70 (80.4%) met the NACI clinical case definition, and 3 (3.4%) met a modified clinical case definition. The median age of the affected students was 16 (range 14 to 19) years versus 17 (range 14 to 21) years for the unaffected students; the mean age in the two groups was similar (16.5 and 16.7 years). The overall attack rate was 7.7%. There were no significant differences in case distribution by age or by sex (RR for female compared with male students 0.82, 95% confidence interval [CI] 0.55 to 1.23). Investigation revealed that, 3 weeks before the onset of symptoms, the index case subject had participated in an event at another school, where several students were in the presymptomatic but infectious phase of measles.

Vaccination status and vaccine efficacy

The overall measles vaccination coverage at the school was high, with 1069 students (94.2%) having been vaccinated at least once before the outbreak, at or after 12 months of age; this includes the 13 students whose first dose was received before 12 months. Of the 87 students with measles 1 was inadequately vaccinated (98.8% coverage). Of the 1048 students without measles 65 were inadequately vaccinated (93.8% coverage). One of the affected students and 102 of the unaffected students had received two doses of measles vaccine at age 12 months or later, before the outbreak (Table 2).

Table 2: Vaccination status of students with and without measles in an outbreak in a Toronto secondary school

Vaccination status	No. (and %) of students			
	With measles	Without measles	Total *n = 1135*	
Never vaccinated	1	38	39	(3.4)
One dose before outbreak [no. before 12 mo of age]	82 [0]	865 [1]	947 [1]	(83.4)
Two doses before outbreak [no. with first dose before 12 mo of age]	2 [1]	114 [12]	116 [13]	(10.2)
Second dose during outbreak	2	5	7	(0.6)
First dose during outbreak	0	26	26	(2.3)
Total	87	1048	1135	

Thirty-nine students, one of whom had measles, never provided documentation of measles vaccination (many of these students, although registered at the school, had dropped out). Although the students without documented vaccination were excluded from school, they may have been exposed before being excluded.

The vaccine efficacy values for the various group comparisons are shown in Table 3.

Risk factors

Among those vaccinated only once, vaccine failure was positively associated with age at vaccination of less than 15 months (RR 3.62, 95% CI 2.32 to 5.66; Table 4). Small cell sizes precluded meaningful analyses for cutoff points under 15 months.

Although the mean interval since vaccination differed significantly between the students with measles and those without measles (15.0 and 13.9 years respectively) ($p = 0.006$), there was no increased risk of vaccine failure associated with a long interval once the RR was adjusted for age at vaccination in a stratified analysis. Vaccination before 1980, when a heat-stabilized vaccine was introduced, and an estimated date of vaccination were not associated with increased risk of vaccine failure.

Two doses of measles vaccine received before the outbreak conferred significant protection, with an elevated RR associated with only one dose (RR 5.0, 95% CI 1.25 to 20.15). The mean age at second vaccination did not differ significantly between the students with measles and those without measles (92.5 and 135.6 months, $p = 0.28$). Administration of a second dose during the outbreak showed a trend toward protection but did not significantly reduce the risk of measles (RR 0.3, 95% CI 0.09 to 1.00). It should be noted that the numbers included in this analysis were small (two students with measles and five without measles).

Based on the current schedule of a single dose of vac-

Table 3: Measles vaccine efficacy estimates*

Comparison	Attack rate; group: Nonvaccinated or less often vaccinated	Attack rate; group: Vaccinated or more often vaccinated	Vaccine efficacy, %
Never vaccinated v. received one dose	0.03	0.09	−200
Never vaccinated v. received two doses	0.03	0.01	67
Received one dose v. received two doses	0.09	0.01	89

*Only students vaccinated at age 12 months or more before the outbreak were included.

Table 4: Risk factors for vaccine failure among students who received one dose of measles vaccine before the outbreak

Risk factor	Students with measles *n = 82*	Students without measles *n = 865*	Significance*
Mean age (and range) at vaccination, mo	17.4 (12–173)	30.9 (8–219)	$p = 0.004$
Age at vaccination, no. of students			RR 3.62†
< 12 mo	0	1	(95% CI 2.32–5.66)
12–14 mo	56	296	
≥ 15 mo	26	568	
Mean interval (and range) since vaccination, yr	15.0 (0–18)	13.9 (0–18)	$p = 0.006$
Interval since vaccination, no. of students			RR 1.24‡
< 15 yr	30	426	(95% CI 0.81–1.89)
≥ 15 yr	52	438	
No. (and %) vaccinated before 1980	35 (42.7)	293 (33.9)	RR 1.18‡ (95% CI 0.78–1.77)
No. (and %) for whom vaccination date was estimated	33 (40.2)	327 (37.8)	RR 1.20‡ (95% CI 0.79–1.82)

*RR = relative risk, CI = confidence interval.
†Comparing age at vaccination of 15 months or more v. less than 15 months.
‡Summary RR, adjusted for age at vaccination.

cine at 12 months of age or later,[21] only one of the cases was preventable (a student born after 1956 with no contraindications to vaccination but nonvaccinated after the first birthday). Age at vaccination and receipt of two doses of measles vaccine significantly altered the measles attack rate in this study. Given otherwise identical conditions, 37 cases (42%) could have been prevented if all the students had received one dose at 15 months of age or later, and 76 cases (87%) could have been prevented if all the students had received two doses before the outbreak, with the first at 12 months of age or later (Table 5).

Discussion

The two factors in our study that significantly altered the measles attack rate were age at vaccination and a history of two doses of vaccine. For students who were vaccinated only once, administration of the vaccine before 15 months of age significantly increased the risk of illness, presumably owing to higher primary vaccine failure rates. Administration of two doses of measles vaccine before the outbreak reduced the attack rate to 1.0%.

The negative vaccine efficacy estimate for the comparison of those never vaccinated with those adequately vaccinated once (at age 12 months or later) does not imply that measles vaccine causes disease. Rather, it reflects a high rate of vaccination and the "apparent paradox of measles infections in immunized persons."[4] When the proportion of a population inadequately vaccinated approximates or is less than the known vaccine failure rate, disease attack rates among those vaccinated are expected to be greater than the attack rates among those not vaccinated, and a negative vaccine efficacy estimate results. With high vaccination rates, measles becomes a disease affecting vaccinated people.

Like all observational cohort studies, ours was limited by the existing sample size. Also, the small number of students who received a second dose of measles vaccine during the outbreak constrained our ability to assess accurately the effectiveness of this strategy. However other investigators have not found such a strategy to be effective.[6]

Case ascertainment may have been incomplete, although the extensive case-finding efforts make this unlikely. We also included three students with a modified case definition of measles (unmeasured temperature) since in the context of this outbreak their illness was almost certainly true measles. The IRIS data were essentially complete. However, for 395 students the date of vaccination was estimated, which implies that, at school entry, the child's measles vaccination was assessed as meeting standard requirements[27] (in most of these records only the day of the month was missing).

We could not assess whether specific lots of vaccine were implicated in the outbreak, as vaccine lot numbers were not routinely provided in vaccine documentation by private physicians. However, the range in age among case subjects and the range in year of vaccination make it extremely unlikely that a bad batch of vaccine was responsible for vaccine failure.

Although it is theoretically possible that earlier detection and intervention in this outbreak could have limited the number of students exposed to measles and hence the number of cases, under the current schedule of a single dose of vaccine at 12 months or more, only one case was "preventable." However, a population-based two-dose measles vaccination strategy could have reduced the number of cases during this outbreak by 87%.

Measles continues to cause considerable illness (and some deaths) among Canadian children. Routine preventive measures are needed if this situation is to change. Two-dose strategies during outbreaks have been shown to be ineffective,[6] and delaying vaccination until 15 months, although an attractive strategy, would leave children aged 12 to 14 months vulnerable at an age when the risk of complications is still high.[26] Ontario and Quebec will soon have mandatory two-dose measles vaccination schedules as a requirement for school entry. Studies such as this one of school-based measles outbreaks in highly vaccinated populations strongly support such a policy if Canada is to achieve its goal of measles elimination by 2005.

We gratefully acknowledge the contributions of the Communicable Disease Control and Epidemiology staff of the Department of Public Health, City of Toronto.

Table 5: Number of preventable cases of measles

Condition	No. of students with measles	No. of students without measles	Attack rate, %	No. of cases expected in total population*	No. (and %) of actual cases preventable†
All students vaccinated once at 15 mo or older before outbreak	26	568	4.4	50	37 (42)
All students vaccinated with two doses before outbreak, with first dose at 12 mo or older	1	102	1.0	11	76 (87)

*The total number of cases expected if all students had received vaccination as specified in the condition column (calculated as the product of condition-specific attack rates and total school population [1135]).
†Measles cases that were considered preventable if all students had received vaccination as specified in the condition column, all other outbreak conditions being identical (calculated by subtracting the expected from the observed number of cases [87]).

References

1. Katz SL, Gellin BG. Measles vaccine: Do we need new vaccines or new programs? [review]. *Science* 1994;265:1391-2.
2. Heisler MB, Richmond JB. Lessons from Finland's successful immunization program [editorial]. *N Engl J Med* 1994;331:1446-7.
3. Consensus conference on measles [review]. *Can Commun Dis Rep* 19/93;19:72-9.
4. Poland GA, Jacobson RM. Failure to reach the goal of measles elimination. Apparent paradox of measles infections in immunized persons [review]. *Arch Intern Med* 1994;154:1815-20.
5. Tulchinsky TH, Ginsberg GM, Abed Y, Angeles MT, Akukwe C, Bonn J. Measles control in developing and developed countries: the case for a two-dose policy [review]. *Bull World Health Organ* 1993;71(1):93-103.
6. Osterman JW, Melnychuk D: Revaccination of children during school-based measles outbreaks: potential impact of a new policy recommendation. *Can Med Assoc J* 1992;146:929-36.
7. Notifiable diseases annual summary. 1993. *Can Commun Dis Rep* 1995;21 (suppl 1):1-75.
8. Summary of reportable diseases quarterly report, 3rd quarter, 1995. *Public Health Epidemiol Rep Ont* 1995;6(12):325-40.
9. Naus M. Ontario school children to be immunized against measles beginning February 1, 1996. *Ont Med Rev* 1995;Dec:1.
10. Shepard DS. Economic analysis of investment priorities for measles control [review]. *J Infect Dis* 1994;170(suppl 1):S56-S62.
11. Yuan L. Measles outbreak in 31 schools: risk factors for vaccine failure and evaluation of a selective revaccination strategy. *Can Med Assoc J* 1994;150: 1093-8.
12. Matson DO, Byington C, Canfield M, Albrecht P, Feigin RD. Investigation of a measles outbreak in a fully vaccinated school population including serum studies before and after revaccination. *Pediatr Infect Dis J* 1993;12(4):292-9.
13. Mast EE, Berg JL, Hanrahan LP, Wassell JT, Davis JP. Risk factors for measles in a previously vaccinated population and cost-effectiveness of revaccination strategies. *JAMA* 1990;264:2529-33.
14. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field: further observations [review]. *Epidemiol Rev* 1988;10:212-41.
15. Judelsohn RG, Fleissner ML, O'Mara DJ. School-based measles outbreaks: correlation of age at immunization with risk of disease. *Am J Public Health* 1980;70:1162-5.
16. Marks JS, Haden GF, Orenstein WA. Methodologic issues in the evaluation of vaccine effectiveness: measles vaccine at 12 vs. 15 months [review]. *Am J Epidemiol* 1982;116:510-23.
17. Orenstein WA, Markowitz L, Preblud SR, Hinman AR, Tomasi A, Bart KJ. Appropriate age for measles vaccination in the United States [review]. *Dev Biol Stand* 1986;65:13-21.
18. Brunell PA, Weigle K, Murphy MD, Shehab Z, Cobb E. Antibody response following measles–mumps–rubella vaccine under conditions of customary use. *JAMA* 1983;250:1409-12.
19. Peltola H, Heinonen OP, Valle M, Paunio M, Virtanen M, Karanko V, et al. The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two-dose vaccination program. *N Engl J Med* 1994;331:1397-402.
20. Ontario and Quebec announce a routine two-dose measles vaccine program and a supplementary catch-up program. *Measles Update* 1995;3(4):1.
21. National Advisory Committee on Immunization. *Canadian immunization guide*. 4th ed. Ottawa: Health Canada, 1993. Cat no H49-8/1993E.
22. *Towards measles elimination bulletin*. Toronto: Ontario Ministry of Health, 1995–96;1(1–9).
23. *Measles elimination in Ontario: information for physicians*. Toronto: Ontario Ministry of Health, 1995.
24. *Towards measles elimination bulletin*. Toronto: Ontario Ministry of Health, 1996;2(1–6).
25. Guidelines for control of measles outbreaks in Canada (revised 1995). Advisory Committee on Epidemiology. *Can Commun Dis Rep* 1995;21:189-95.
26. Committee on Infectious Diseases, American Academy of Pediatrics. *1994 red book: report of the Committee on Infectious Diseases*. 23rd ed. Elk Grove Village (IL): The Academy, 1994:308-25.
27. *Ontario Immunization of School Pupils Act*, RSO 1990, c I.1.
28. Pasut G. Reportable diseases in Ontario. *Public Health Epidemiol Rep Ont* 1991;Feb:15.
29. *Health Protection and Promotion Act*, RSO 1990, c H.7.